Prodrug innovation to target muscle stem cells and enhance muscle regeneration

Grant Award Details

Prodrug innovation to target muscle stem cells and enhance muscle regeneration

Grant Type: Inception - Discovery Stage Research Projects

Grant Number: DISC1-10036

Project Objective: To develop biological tools that can target therapeutics to muscle stem cells

Investigator:

Name:	Helen Blau
Institution:	Stanford University
Type:	PI

Disease Focus: Skeletal Muscle

Award Value: $235,834

Status: Active

Grant Application Details

Application Title: Prodrug innovation to target muscle stem cells and enhance muscle regeneration

Public Abstract:

Research Objective

To target therapeutics to muscle stem cells, the building blocks of skeletal muscle.

Impact

Drugs, genes and gene editing strategies can be delivered directly to muscle stem cells to alleviate disease.

Major Proposed Activities

- Synthetic peptides based on the ectodomains of Myomaker will be synthesized, with a fluorophore conjugated for tracking. Alternatively, anti-Myomaker sdAbs will be developed to target MuSCs.
- Peptides or sbAb from Activity 1 will be tested in vitro for binding against isolated mouse and human MuSCs, as well as other cell types to assess targeting specificity.
- The optimized targeting moiety from Activity 2, will be delivered via intramuscular injection to a myotoxin-injured hindlimb muscle in mice to assess in vivo MuSC-targeting.
- A prodrug will be synthesized by conjugating the optimized targeting moiety with SB202190, a drug known to rescue the regenerative capacity of aged MuSCs.
- Bioactivity of the SB prodrug will be assessed in vitro in isolated mouse and human MuSCs, using known biomarkers including phosphorylation of p38α/β and MK2.
- For clinical indications, the SB prodrug treatment will be tested in a mouse myotoxin-induced muscle injury model. Muscle regeneration and functional recovery will be assessed.

Statement of Benefit to California:

Skeletal muscles are critical for all voluntary movements. Muscle deterioration due to aging or genetic disorders often leads to grave physical disability and diminished quality of life. Combined, muscle disorders impose a significant economic burden of over $18B/year in the U.S. Currently, there exists no means of targeting muscle stem cells, the engines of muscle tissue growth and repair throughout life. We will meet this need and increase the efficacy and safety of muscle therapeutic agents.
